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EXAMINER	
KWON, BRIAN YONG S	
ART UNIT	**PAPER NUMBER**
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/813,760	BERNSTEIN, JOEL E.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02/28/07*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 11-37* is/are pending in the application.

4a) Of the above claim(s) *16-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 11-15* is/are rejected.

7)☐ Claim(s) _ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. Acknowledgement is made of applicant's filing of an amendment/remarks on 02/28/07. By the amendment, claims 1, 13, 24 and 30 have been amended and claim 10 has been cancelled. Claims 1-9 and 11-15 are currently pending for prosecution on the merits.

2. Applicant's arguments have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of actions being applied to the instant application.

3. Applicant's amendment changing the scope of the invention by reciting "consisting essentially of" necessitates a new ground of the rejection in this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-9 and 11-12 are rejected under 35 USC 112, first paragraph, because the specification while being enabling for the specific hepatotoxic compound such as acetaminophen, methotrexate, atorvastatin, simvastatin, niacin, fluconazole, divalproex sodium and valproic acid, does not reasonably provide enablement for "a hepatotoxic compound". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: the nature of the invention; the state of the prior art; the relative skill of those in the art; the predictability or unpredictability of the art; the breadth of the claims; the amount of direction or guidance presented; the presence or absence of working examples; and the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The present invention is drawn to a composition one or more of hepatotoxic compound, about 5mg to about 500 mg of methionine and about 10mg to about 500mg of nicotinamide.

The interpretation of the instant claims allows for the inclusion of any known hepatotoxic compound or drug that are known to exist and those that may be discovered in the future.

The relative skill of the artisan and the unpredictability of the pharmaceutical art is very high. To practice the instant invention to the claimed scope, applicant would have to (i) screen numerous possible compounds characterized as "hepatotoxic compound, (ii) assay to find out which compounds are able to induce hepatotoxicity at what concentration level and then (iii) extrapolate the test and result to the claimed invention. In other words, the instant invention necessitates for the skilled artisan to undergo an exhaustive search for the embodiments suitable to practice the claimed invention.

Where the physiological activity of a chemical or biological compound is considered to be an unpredictable art (Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of

the factors involved". See In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970)), the skilled artisan would have not known how to extrapolate the examples provided in the instant specification ("acetaminophen, methotrexate, atorvastatin, simvastatin, niacin, fluconazole, divalproex sodium and valproic acid" are set forth as suitable working examples) to the larger and highly varied genera of compounds that are characterized by "hepatotoxic compound", without undue amount of experimentation.

As discussed above, given the breadth, the disparate nature of compounds that is presently claimed, the highly unpredictable state of the art, and the insufficient amount of guidance present in the specification, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to make/use the claimed "hepatotoxic compound" that would be enabled in this specification (The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in the determining whether is required to make and use the instant invention. "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976))).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-9 and 11-15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The amended claim, particularly independent claim 1, recites transitional phrase "consisting essentially of" which limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. The recitation of transitional phrase "consisting essentially of" followed by "comprising" or "contains" (which leaves the "claim open for the inclusion of unspecified ingredients in major amounts") leaves the reader in doubt as to the meanings of the invention to which they refer, thereby rendering the definition of the subject matter of said claims unclear.

In other words, the applicant's recitation of "comprising" or "contains" with the term "consisting essentially of" improperly broadening out the scope of the instant composition, and thus renders the scope of the claim unascertainable.

If the claimed invention is construed to mean "exclusion of the specified materials or steps and those that materially affects the basic and novel characteristics", the extra components that are being incorporated into the composition must show that it would not materially change the invention. However, the dependent claim 7 introduces the additional component such as folic acid that is known to affect the basic and novel characteristics of the composition. The specification discloses that the addition of folic acid to the composition further mitigates the hepatotoxic properties (para. [0007]).

As discussed above, it is clear that the instant term "consisting essentially of" allows for the inclusion of other ingredients or components that materially affect the basic and novel

characteristics of the claimed composition, and thus is interpreted as fully open transitional phrase.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 1-9 and 11-15 are rejected under 35 U.S.C. 102(e) as being anticipated by Summers (US 6733797 B1).

Summers teaches a composition comprising chromium or curcuma (which is known to have hepatotoxic property), 111 mg (or 0-1500mg) of methionine, 23.1mg (or 0-1000mg) of niacinamide (also commonly known as nicotinamide or vitamin B3) and 180mcg (or 0-250 mcg) of folic acid (see Tables 1 and 2), wherein said composition is prepared in suitable dosage forms including oral, parenteral, rectal and topical forms (column 3, lines 65-67 and claims 1 and 3).

Since the interpretation of the instant claims allows for the inclusion of any other unspecified ingredients even in major amounts in said composition, Summers anticipates the instant invention.

With respect to the limitations in claims 3-6 and 9-12, the referenced parenteral administration (Webster's II dictionary defines the term "parenteral" as "taken into the body or administered in manner other than through the digestive tract, as by intravenous or intramuscular

injection") "metes and bounds" the instantly claimed "solutions, suspensions...", "injection", "sterile solutions or suspensions" or "...intramuscular, intravenous...". Therefore, Summers anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kroger et al. (Gen. Pharmac., Vol. 28, No. 2, pp. 257-263, 1997) and further in view of Yang (US 5474757).

Kroger teaches use of combination of nicotinamide (12.5mg/kg IP or from 25 mg/kg to 100mg/kg IP) and methionine (12.5mg/kg IP or from 25 mg/kg to 100mg/kg IP) in decreasing hepatotoxicity induced by the hepatotoxic compound such as 500mg/kg of acetaminophen (abstract; Figure 2; Results; Discussion).

Yang teaches a composition comprising acetaminophen, organosulfur compound and methionine (claims 17 and 21), wherein said acetaminophen is present in dosage amounts of "from 0.04 mg/kg/day to about 50 mg/kg/day" in various dosage forms including tablets, gelcaps, capsules, caplets, granules, solution, suspension or injectable forms, for example "80mg, 325mg, 500mg, and 650mg" in oral solid dosage forms, "100 mg/ml, 120 mg/2.5 ml, 120 mg/5 ml, 160 mg/5 ml, 165 mg/5 ml, 325mg/5 ml" in oral liquid dosage forms (column 9, line 5 thru column 10, line 11); . Yang teaches the use of methionine as protective agent for acetaminophen overdose (column 2, lines 4-6; claims 17 and 21).

Kroger differs from the claimed invention in the preparation of a composition comprising acetaminophen, nicotinamide and methionine in the specific amounts, namely about 80-1000 mg dose of acetaminophen, about 5 mg to about 500 mg dose of methionine and about 10 mg to about 500 mg dose of nicotinamide, per standard dose.

However, it would have been prima facie obvious, within the meaning of 35 USC 103, to employ the components in combination for their known functions. One having ordinary skill in the art would have expected as based upon the prior art and the fact that each of the three

components of the composition used in the claimed invention is conventionally employed in the art for reducing acetaminophen overdose hepatotoxicity.

One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

With respect to the determination of the specific dosage amounts of each ingredient in said composition, those of ordinary skill in the art would have been readily optimized effective dosages as determined by good medical practice and the clinical condition of the individual patient. Regardless of the manner of administration, the specific dose would have been calculated according to body weight, body surface area or organ size. Further refinement of the calculations necessary to determine the appropriate dosage for treatment involving each of the above mentioned formulations would have been routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, especially in light of the dosage information disclosed in the prior art references.

Response to Arguments

8. Applicant's arguments filed 02/28/07 have been fully considered but they are not persuasive.

Applicant's argument in the response takes the position that the instant composition excludes a phosphoester and an antioxidant required by Summers. The applicant alleges that the instant application requires a hepatotoxic compound in its composition whereas no hepatotoxic compound is taught or claimed as part of the composition described in USP'797.

This argument is not found persuasive at all. As discussed above, the applicant's term "consisting essentially of" allows for the inclusion of other ingredients or components that materially affect the basic and novel characteristics of the claimed composition, and thus is interpreted as fully open transitional phrase like "comprising". Thus, the examiner maintains that Summer's formulation containing phosphesters and antioxidants "metes and bounds" the claimed invention.

Alternatively, even if the examiner interprets the term "consisting essentially of" as to the scope of a claim to the specific materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention, the applicant fails to show that the components recited in USP'797 such as phosphoesters and antioxidants would materially change the invention. In absence of the applicant's showing that the introduction of steps or components would materially change the invention, the examiner maintains the rejection of record.

In response to the applicant's argument that there is no teaching in USP'797 of the use of hepatotoxic compound, the examiner recognizes the known hepatotoxic property of chromium or curcuma (see "Sublethal effects of hexavalent chromium on the body growth rate and liver function enzymes of phenobartione-pretreated and promethazine-pretreated rabbits", Anjum et al., J Environ Pathol Toxicol Oncol, abstract, 1997, 16(1):51-9; "Nephrotoxic and hepatotoxic effects of chromium compounds in rats", Laborda et al., abstract, Bull Environ Contam Toxciol, 1986, 36(3):332-6; and "As evidence-based systemic review of herb and supplement interactions by the natural standard research collaboration", Ulbricht et al., Expert Opinion, 2006, 5(5);719-728, which were attached with the previous PTO-892 mailed 11/29/2006)

In response to applicant's argument that the Kroger does not teach that much lower dosages of nicotinamide and methionine, administered in a single dosage form with a hepatotoxic drug, given by completely different routes of administration than Kroger, would provide safe and effective hepatoprotection from a hepatotoxic drug.

This argument is not found persuasive. Unlike the applicant's argument, there are general references (see USP 6733797 B1; USP 6048846; USP 4581348; USP 4401657; USP 4837239; Kegon'kova et al., Eksp. Klin Farmakol., 1997, abstract, 1997, 60(2):68-71) indicating that pharmaceuticals containing nicotinamide and methionine alone or in combination generally may be delivered orals, as well as disclosing benefits to be achieved by orals versus other modes of administration (i.e., parenteral). Therefore, there exist general art accepted motivations for formulating drugs for oral administration. Furthermore, determination of appropriate dosage amounts for treatment of intended purpose involving each of the above mentioned formulation is routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, especially in light of the prior art (see also USP 6733797; USP 4581348; USP 6048846). Thus, the examiner maintains the rejection of the record.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. No Claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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